FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee
May 5, 2005
NDA 21-824

Questions to the Committee

Background

Zarnestra is a farnesyl transferase inhibitor that has been evaluated in a number of clinical studies, including studies in patients with acute myelogenous leukemia (AML).

The sponsor is proposing the following indication based on this NDA submission: " For the treatment of elderly patients with newly diagnosed poor-risk acute myeloid leukemia."

The clinical database for this NDA included several single arm trials. CTEP-20, which enrolled a total of 171 patients with previously untreated hematologic malignancies, is the most relevant to the indication proposed. After 110 patients had been enrolled, the eligibility criteria were modified to specify age 75 or older with untreated AML or age 65 to 74 years with AML arising from prior myelodysplastic syndrome (MDS).

FDA assessment of eligibility criteria and demographic datasets results in identification of 135 patients with AML age 65-74 with prior MDS or age 75 and older.

Based on the primary endpoint of complete remission rate and the secondary endpoint of response duration, FDA assessment results in the following findings:

Confirmed CR rate = 11.1% (15/135) with 95% C.I. 6.6%-18%
Median duration of remission 275 days with 95% C.I. 127 days – 376 days

Safety evaluation of the elderly poor-risk AML population of CTEP-20 (N = 136, included one patient not included in FDA efficacy analysis due lack of criteria for AML at baseline) can be summarized as follows:

Ninety-eight percent of the 136 patients experienced adverse events. The most frequent treatment emergent grade 3 or 4 adverse events included neutropenia with or without fever (41%), infections (27%), thrombocytopenia (17%), anemia (8%), fatigue (13%), rash (9%), dyspnea (8%) and confusion (7%).

Adverse events leading to change in treatment included increased creatinine, rash and neutropenia.

Thirty-one (23%) of the 136 patients died within 30 days of first dose of medication or within 30 days of treatment termination. The death rate within 30 days of the first dose was 12% in this population, and the death rate due to adverse events was 7%.

Background (cont)

Comparison of these findings with reported literature describing outcome of therapy in elderly AML patients receiving chemotherapy can be summarized as follows. It should be noted that these two populations are not entirely comparable with respect to age and other factors since the 'chemotherapy' population includes those age 60 or older with adequate organ function to receive chemotherapy.

Outcome	**Zarnestra**	**Chemotherapy**
Complete remission rate	11.1%	30%-50%
Treatment-related deaths	7%	> 25%
One-month mortality	12%	30-48%

Question

Does the risk benefit analysis support regular approval of Zarnestra for the first-line treatment of AML patients age 65 or older with prior MDS or age 75 and older?